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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

O HARA, EILEEN B

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 06/18/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/895,298

Applicant(s)

RUBEN ET AL.

Examiner

Eileen O'Hara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 April 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 25-74 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 25-74 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) ✓
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Claims 25-74 are pending in the instant application. Claims 29, 34-35, 37, 42, 44, 49, 51, 56, 58, 62-63, 65-66, 68 and 70-73 have been amended and claims 1-24 have been canceled as requested by Applicant in Paper Number 8, filed April 1, 2003.

Election/Restriction

2. Applicant's election with traverse of Group I in Paper No. 8 is acknowledged. The traversal is on the ground(s) that to search Groups I-VIII would not be a serious burden on the examiner, and that a search of the polynucleotide claims would overlap with that of a search of the polypeptide and related antibodies. This is not found persuasive because consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof; (B) a separate status in the art when they are classifiable together; (C) a different field of search. These criteria were met in the above restriction. A search for antibodies to a protein would constitute a different search than that of a search for the protein. It is old and well known in the art that antibodies have been generated without having purified protein, and antibodies to one protein may also cross-react with a related protein. As stated in the MPEP § 803, "a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02." Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. Thus, the groups require divergent searches, and to search all inventions would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

All pending claims are currently under examination.

Priority

3. Applicants' amendment to the specification to update the current status of the nonprovisional parent application is acknowledged.

Withdrawn Objections and Rejections

4. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

- 6.1 Claims 25-74 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record in the previous Office Action, Paper No. 7, at pages 4-6, and below.

Applicants traverse the rejection and submit that the proper legal standard for evaluating enablement, as cast by the C.C.P.A. and the Federal Circuit, is whether proteins encompassed by the claims have at least a single use, and this use can be confirmed, without undue experimentation, by following procedures either described in the specification or otherwise known in the art, and cite *In re Angstadt* and *In re Fisher*. Applicants assert that it would not

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require undue experimentation on the part of one of ordinary skill in the art to use the polypeptide of the present invention as a diagnostic marker for cancer, and point to a statement in the specification at page 66, and assert that this can be done by comparing expression levels of the gene encoding the claimed polypeptide in diseased tissue relative to the levels from healthy non-diseased tissue. Applicants assert that the specification clearly indicates that the gene encoding the polypeptide of SEQ ID NO: 83 is primarily expressed in ovarian cancer, and that based on a reasonable reading of "primarily" one of ordinary skill in the art would conclude that the gene encoding the polypeptide of SEQ ID NO: 83 is overexpressed in cancerous ovarian tissue, and that it is apparent that the claimed polypeptide would be expressed differentially in ovarian cancer tissue relative to normal healthy tissue. Applicants further assert that the "Guidelines for Marker Development" by the NCI is wholly inadequate to establish that one skilled in the art would conclude, under the law, that the claimed polypeptides are not useful or enabled as an ovarian cancer diagnostic, and that the draft document was prepared to help evaluate whether markers or assays are ready for use in clinical settings, and that this is not the standard required for patentability under 35 U.S.C. §§ 101 or 112. Applicants further assert that the Draft Guidelines are merely a draft promulgated well after the priority date of the instant application and therefore do not reflect what the skilled artisan would find credible or enabling on December 17, 1998, the priority date of the present application, and that the fact that the NCI felt the need to draft these guidelines, tends to suggest that skilled artisans often concluded that markers were credibly useful and thus well enabled before large statistical studies were performed on a heterogeneous population. Applicants cite *In re Marzocchi* and assert that the

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Patent Office must take as enabling a patent Applicant's specification disclosure that contains a teaching of how to make and use the invention.

Applicants' arguments have been fully considered but are not deemed persuasive. While there is no reason to doubt the assertion that the gene encoding the polypeptide could be used as a cancer marker and is therefore credible, this is not sufficient to enable the use of the polypeptide. The specification states that the gene is expressed primarily in ovarian tissue, and to a lesser extent in breast cancer and prostate tissue. However, absent information on how many tissue samples were analyzed, and the degree of expression in cancer tissue relative to normal tissue, one of ordinary skill in the art would not conclude that this gene or encoded polypeptide would be useful as cancer markers. Studies using small patient populations provide useful information on usefulness of cancer markers. Ferrari et al., Journal of the National Cancer Institute, Oct. 15, 1997, compared pathologic examination of fifty-eight pelvic lymph nodes from 33 patients with localized prostate cancer that exhibits high-risk features with reverse transcription-polymerase chain reaction (RT-PCR) methods. Relapse in these types of patients (that do not have pathological lymph node involvement at time of local therapy) is 55-92% within five years. Expression of prostate specific antigen (PSA) and prostatespecific membrane antiben (PSM) messenger RNAs in the specimens were assessed and compared to pathologic examination of the same specimens. Pathologic examination identified tumor cells in only 4 (12%) of the 33 patients, while PSA and/or PSM expression was positive in specimens from 27 (82%) of the patients, demonstrating that these markers are useful in identifying metastatic tumor cells in patients in which pathologic examination is negative. However, PSM expression was detected more frequently than PSA expression, and in two patients, only PSA expression was

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detected. This is evidence of the variability of expression of cell-specific markers, and that even well-established markers for a specific cell type is not always expressed. Even established cancer markers in use in clinical settings are not necessarily expressed in all instances of cancer. Clark et al. (British Journal of Cancer, 1999), examined the potential role for prolactin-inducible protein (PIP) as a marker of human breast cancer micrometastasis, using tissue from 97 primary breast tumor samples, in six human breast cell lines, and normal peripheral blood lymphocytes. Five human breast cancer cell lines and one normal human breast cell line were analyzed for expression of PIP, and 3 out of the five breast cancer lines showed positive expression, while two did not, and the normal breast cell line also showed positive expression (see materials and methods, and page 1005, first column, first full paragraph). From their results, the authors concluded that the PIP gene has potential as a marker of breast micrometastasis because PIP is expressed by most primary breast tumors and expression is often conserved in nodal metastases, and is not expressed in several tissues that are often targets of breast tumor metastasis, but that in common with several other genes proposed as tumor markers, their results demonstrate the potential for false-negative and false-positive results (see page 1007, last paragraph of discussion).

From these teachings, one of ordinary skill in the art recognized at the time of filing of the instant application that a minimal number of samples must be analyzed before concluding that a particular gene would be useful as a cancer marker. Contrary to Applicants argument, the determination of a cancer marker must be based on studying results from a considerable number of patients, and statistical analysis. The specification does not present any information on how many samples were analyzed, or the extent of expression. In the instant case, the expression of

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the gene in ovarian cancer tissue suggests certain possible potential of the protein as a cancer marker, which, at the most, is an interesting invitation for further research and investigation, and by no means can be claimed as a marker for ovarian cancer. Upon further research, such as studying an increased number of patients, and performing the statistical analysis on the collected data, this gene may be useful as a cancer marker. This further characterization, however, is part of the act of invention, and until it has been undertaken, the claimed invention is incomplete.

The issue is the general principle applied in the art for determination of a marker, which requires the frequency data, and the present application does not provide such. As so, a correlation between the presence of polypeptide and ovarian cancer cannot be established. Therefore, one of ordinary skill in the art would not conclude that the gene could be used diagnostically for ovarian cancer.

6.2 Claims 37-64 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record in the previous Office Action, Paper No. 7, at pages 7-9, and below.

Applicants' amendment has overcome the rejection for previously rejected claims 11, 12, 16 and 65-74. Applicants traverse the rejection and assert that they have amended claims 65, 66, 70 and 71 to recite the phrase "consisting of" rather than "comprising", and that pending claims 37-64 recite polypeptides consisting of variants with a functional limitation. Applicants assert that in an analysis of written description under 35 U.S.C. § 112, first paragraph, the Examiner bears the initial burden of presenting a *prima facie* case of unpatentability, and that the Examiner

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has not meet this burden. Applicants cite *in re Wertheim, Amgen, Inc. v. Chugai Pharmaceutical Co., Vas-Cath Inc. v. Muhurkar, Union Oil Company of California v. Atlantic Richfield Company and University of California v. Eli Lilly*, as support for their position that one skilled in the art could reasonably conclude that the inventor had possession of the polypeptides encompassed by the rejected claims in the present application as filed, and that Applicants recognize that the Examiner is in part relying on language regarding a “representative number” of a claimed genus set forth in *Regents of the University of California v. Eli Lilly & Co.*, and incorporated into the Guidelines for Examination of Patent Applications. Applicants assert on page 15 of the response that in the instant case, the second test set forth in *Eli Lilly* has been satisfied because Applicants’ description of the reference polypeptide, SEQ ID NO: 83, provides one of skill in the art with the necessary structural features common to a substantial portion of the members of the genus, and that the recitation of the structural features of the reference protein is a recitation of the structural features common to the members of the claimed genus because the proteins included within the claimed genus will have at least 90% (or at least 95%) of the amino acids of their primary structure in common to the reference polypeptide of SEQ ID NO: 83.

Applicants’ arguments have been fully considered but are not deemed persuasive. Although Applicants assert that claims 37-64 have been amended to recite polypeptides consisting of variants, it is the second polypeptide (SEQ ID NO: 83) that is consisting of, and not the claimed variants. The written description guidelines indicate that a representative species may be adequately described through its structure, through its functional characteristics, or through a combination of its structure and function. Only one sequence has been disclosed, and

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there is no real functional limitation in the claims. The claims do not provide adequate structure or function to meet the written description guidelines. Therefore, the rejection is maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

7. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner


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